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FORMULATION AND *IN VITRO* EVALUATION OF ACECLOFENAC FAST DISSOLVING TABLETS

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ABSTRACT

The objective of the present study was to prepare the Fast Disintegration Tablets of Aceclofenac, which is a used for treatment of non-steroidal anti-inflammatory. Aceclofenac is poorly soluble and its absorption is dissolution rate limited. Dispersions prepared by melting method show better dissolution profile than dispersions prepared by melt solvent method and physical mixture. This may be due to grinding; there is a uniform distribution of drug in the polymer crust at molecular level in a highly dispersed state. Thus, when such system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increases the dissolution surface available. There is an enhancement of dissolution of Aceclofenac on increasing the concentration of Mannitol. The tablets was prepared by direct compression method and evaluated for hardness, friability, weight variation, wetting time, disintegration time and uniformity of content. Optimized formulations were evaluated for *in vitro* dissolution test. Amongst all formulations, formulation F4 prepared by drug: Mannitol (1:4) which is prepared by melt method with croscarmellose sodium showed least dispersion time and faster dissolution. These results indicate that the selected formulation was stable during the period of accelerated stability studies.

KEYWORDS

Aceclofenac, Superdisintegrants, Melting method, Direct compression method and Fast disintegration tablets.

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INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient

compliance. Also solid oral delivery systems do not expensive to manufacture[1]. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs are predominantly protein or peptide based, tablets may no longer be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide[2-4]. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[5, 6]. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Because of the increase in the average human life span and the decline with age in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid require sterile conditions and are therefore, less swallowing. The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". A fast dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[7]. Less frequently, they are designed to be absorbed through the Buccal and esophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast dispersing formulations may be even greater than that observed for standard dosage forms.

MATERIAL AND METHODS

MATERIALS

Aceclofenac was obtained as a gift sample from Amoli organics ltd. Mannitol as a gift sample from Qualigens Fine Chemicals., Mumbai. Cross caramellose, Sodium starch glycolate, Cross povidone as a Gift sample from KAPL, Bangalore All the ingredients used were of analytical grade.

METHODS

Preparation of fast dissolving tablets by direct compression method

All the ingredients, except drug complex was passed through mesh #30 and drug complex were passed through mesh #40. MCC were load into the polyethylene bag and mix for 10 min and Magnesium stearate, croscarmellose, SSG, Crospovidone and aerosil were mixed for 5 min. To the diluent mixture, drug complex was addedand to this add lubricants and disintegrates mixture and mixed for 10 min. The prepared blend was subjected to pre-formulation studies such as micromeritic

properties and was compressed by using 12-station rotary press (Table No.1).

EVALUATION PARAMETERS

Pre-formulation Studies

Drug-polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Aceclofenac and the selected polymers. The pure drug and drug with excipient were scanned separately. Procedure: Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Aceclofenac was compared with FT-IR spectra of Aceclofenac with polymers.

Pre-compression studies of fast dissolving tablets

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M / Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M / Vt$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\text{Tan } \theta = h/r$$

Therefore $\theta = \text{Tan}^{-1} h/r$

Where, θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's compressibility index (\%)} = [(D_t - D_b) \times 100] / D_t$$

Where, D_t is the tapped density

D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausners ratio} = D_t / D_b$$

Where, Dt is the tapped density,

Db is the bulk density.

Post compression studies of Aceclofenac fast dissolving tablets

Measurement of tablet hardness[8]

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Weight variation test[8]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Friability test[8]

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability

by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Disintegration Time

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 liter beaker of distilled water at 37± 2^{o}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Estimation of drug content

From each batch of prepared tablets, ten tablets were collected randomly and powdered. 50 mg of powder, which was equivalent to 10 mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in pH 6.8 phosphate buffers. For both the sample and standard solutions absorbance was measured at 275 nm in UV-Visible spectrophotometer.

Uniformity of dispersion

Two tablets were kept in 100 ml of water and gentle stirred for 2 min. the dispersion was passed through #22 meshes. The tablets were considered to pass the test if no residue remained on the screen.

***In vitro* dissolution**

The prepared tablets were subjected to *in vitro* dissolution. Dissolution test was carried out using USP23 paddle method [apparatus-2]. The stirring rate was 50 rpm, pH6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5 ^{0}C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Aceclofenac at 275 nm by using UV-visible spectrophotometer.

Stability studies

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists detoriation. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Detoriation of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

RESULTS AND DISCUSSION

Pre-formulation Studies

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Aceclofenac were found to be unaltered in the spectra of the drug-polymer physical mixture(Figure No.1 and 2).

Pre-compression Studies

All the formulations prepared by both the methods showed the angle of repose less than 30^{o}C, which reveals good flow property (Table No.2). The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.59 gm/cm^3 to 0.686 gm/cm^3 and 0.635 gm/cm^3 to 0.756 gm/cm^3 respectively (Table No.2). The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 13.24 to 17.15%.

Post-compression Studies

The hardness values ranged from 3.50 to 5.95 kg/cm^2 for formulations were almost uniform.

Tablet hardness is not as absolute strength (Table No.3).

Friability values were found to be within the limit. Thus tablets possess good mechanical strength (Table No.3).

All the tablets passed weight variation test as the average percentage weight variation was within the pharmacopoeia limits of 7.5% (Table No.3).

The drug content (Table No.3) of the tablets was found to be between 97.5 to 100 %. The results were within the range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the average drug content present in the tablet (Table No.4, Figure No.3).

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration ingredients are suggested to be the mechanism of disintegration.

Stability studies were performed as per ICH guidelines on F4, the ACE content varied slightly periodically. The drug release rate was good when stored under accelerated condition (Table No.5, Figure No.4). All the parameters tested, are within the acceptable limits and found to be suitable formulation the fast release of ACE.

Table No.1: General composition of formulation prepared by direct compression method

S.No	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
1	ACE	100	100	100	---	---	---
2	ACE: Mannitol (1:4)	---	---	---	500	500	500
3	MCC(Avicel PH 102)	440	440	440	40	40	40
4	CCS	48	---	---	48	---	---
5	SSG	---	48	---	---	48	---
6	CP	---	---	48	---	---	48
7	Aerosol	6	6	6	6	6	6
8	Magnesium stearate	6	6	6	6	6	6
	Total	600	600	600	600	600	600

Table No.2: Results of flow properties of fast dissolving tablet (F1 to F6)

S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hauser's ratio
1	F1	17.16	0.610	0.741	14.86	1.17
2	F2	22.74	0.590	0.685	13.24	1.16
3	F3	20.70	0.640	0.667	15.28	1.15
4	F4	24.65	0.621	0.756	17.15	1.12
5	F5	24.72	0.652	0.653	15.67	1.14
6	F6	25.89	0.686	0.635	14.59	1.18

Table No.3: Weight variation, Disintegration, Hardness, Friability, and Drug content (F1 to F6)

S.No	Formulation code	Weight Variation (%)	Disintegration (sec)	Hardness (kg/cm^3)	Friability (%)	Drug content(%)
1	F1	98.5	124	5.26	0.96	99.5
2	F2	99.5	190	5.95	0.40	100
3	F3	99.0	214	5.58	0.78	99
4	F4	99.5	58	3.50	0.40	99
5	F5	98.5	78	3.75	0.60	98.1
6	F6	97.5	70	3.50	0.68	97.5

Table No.4: *In vitro* Dissolution data of Aceclofenac fast dissolving tablet

S.No	Time (min)	Cumulative % drug release					
		F_1	F_2	F_3	F_4	F_5	F_6
1	0	0	0	0	0	0	0
2	5	27.48	26.28	25.80	47.80	46.10	45.80
3	10	33.56	31.82	30.12	60.24	56.18	55.18
4	15	38.12	37.98	36.00	70.18	68.10	62.20
5	30	45.45	50.24	48.24	93.92	90.28	88.88
6	45	52.85	53.84	50.26	99.22	98.18	97.18
7	60	68.12	63.10	62.18	----	----	----

Table No.5: *In vitro* release profile of F4 during stability studies (40°±2°c/75%±5% RH)

S.No	Time (min)	Cumulative % drug release			
		Initial	1 month	2 month	3 month
1	0	0	0	0	0
2	5	47.80	46.85	45.12	44.23
3	10	60.24	59.45	58.65	57.56
4	15	70.18	68.91	67.31	66.19
5	30	93.92	93.24	92.61	92.01
6	45	99.22	97.41	96.56	96.01

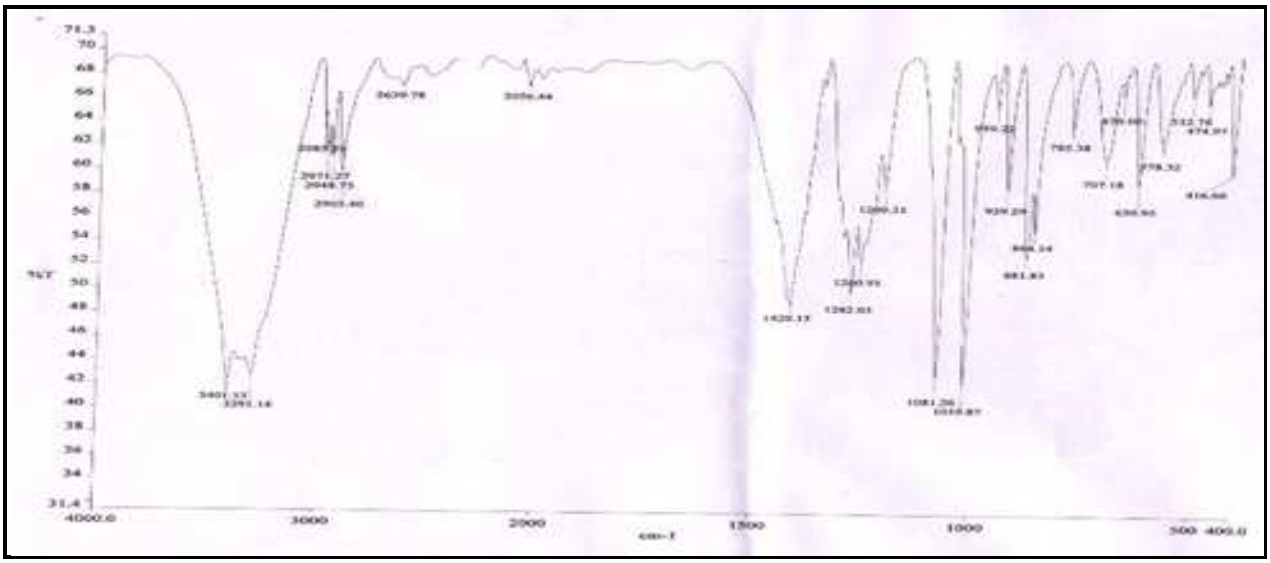

Figure No.1: FT-IR spectra of pure Aceclofenac

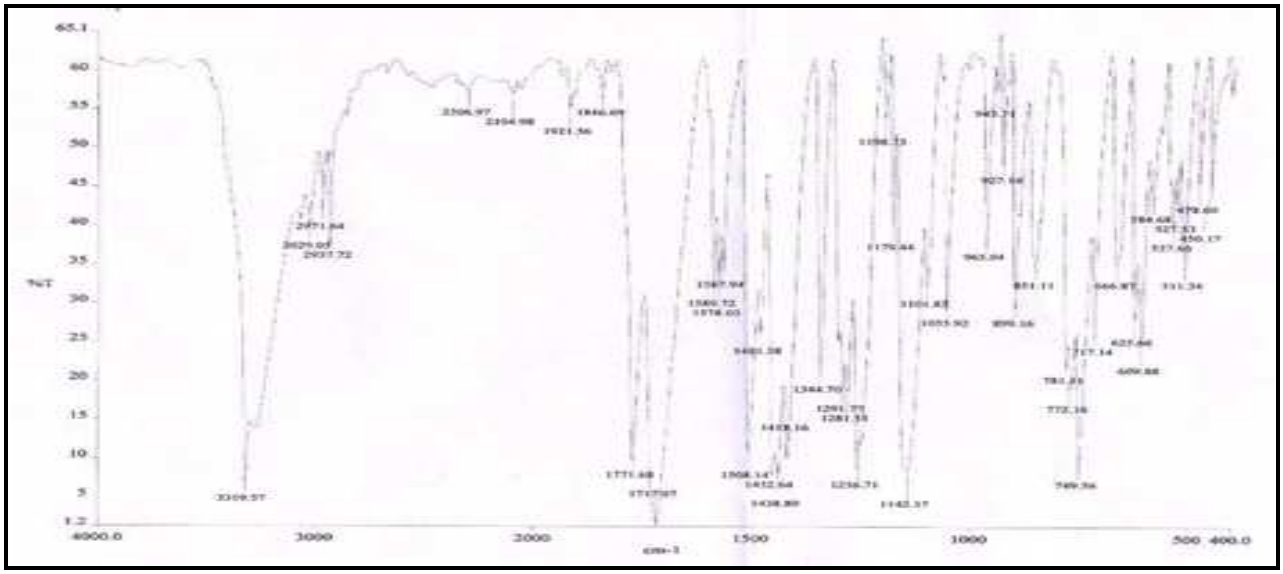

Figure No.2: FT-IR spectra of pure Mannitol

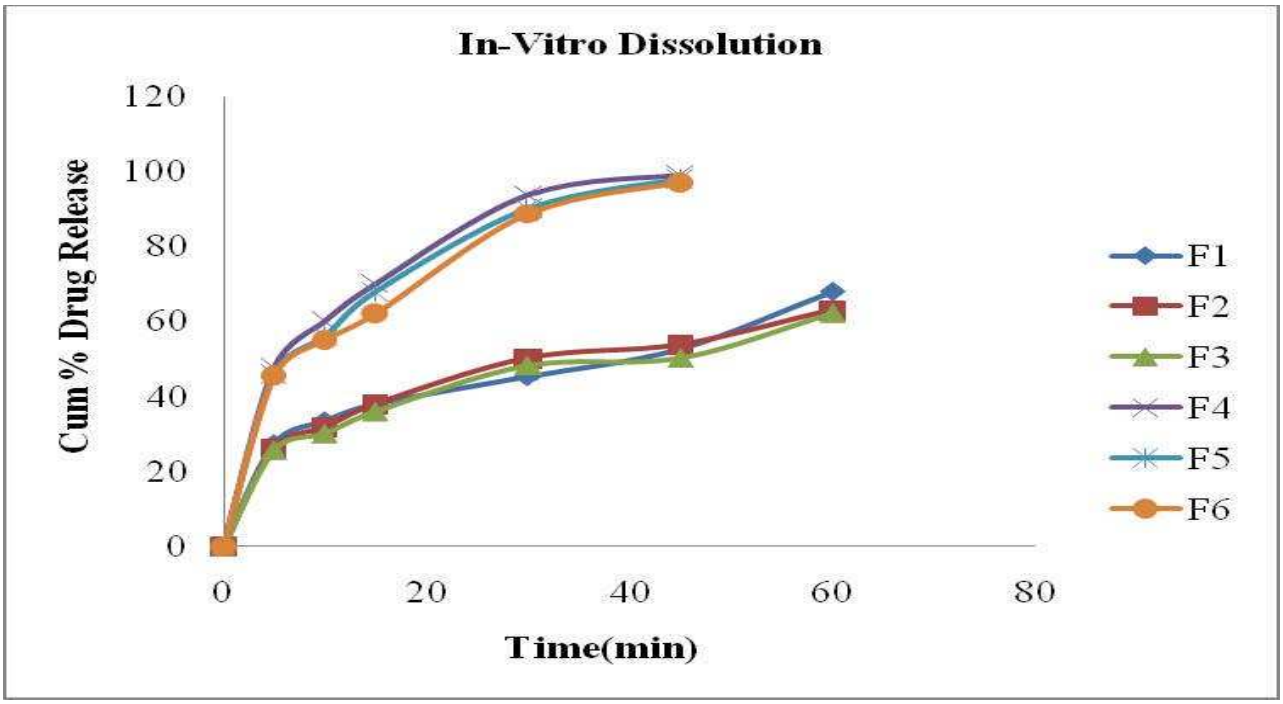

Figure No.3: *In vitro* dissolution profiles for F1 to F6 batches by direct compression method

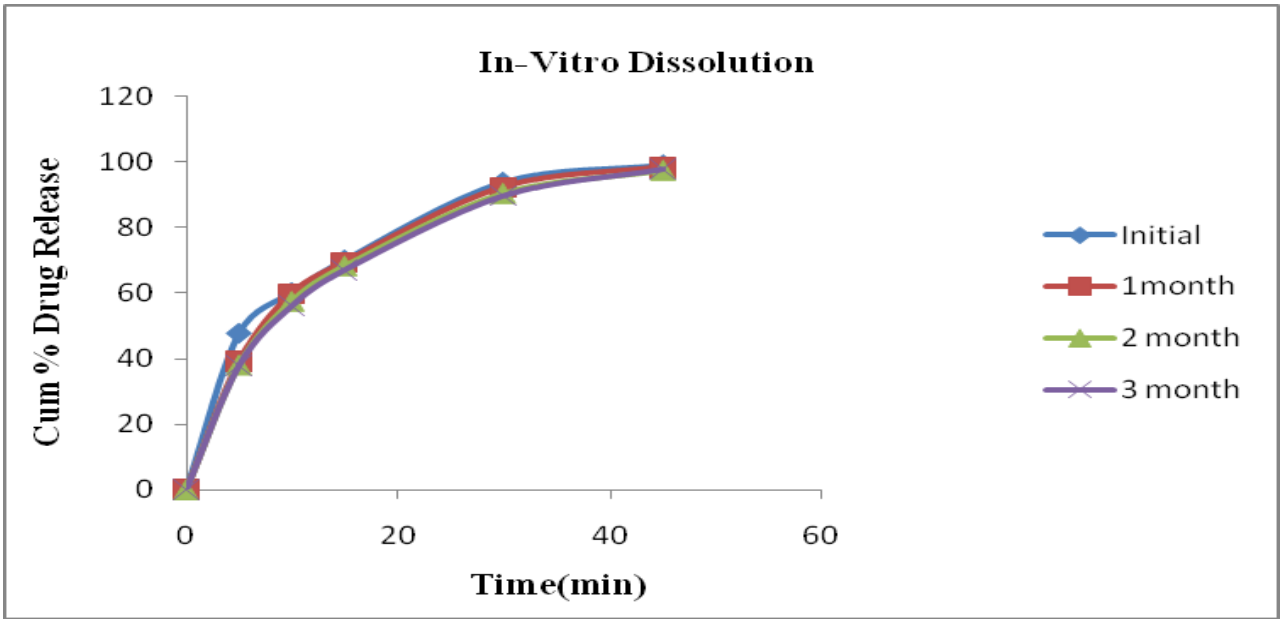

Figure No.4: *In vitro* release profile of F4 during stability studies (40 ^{0}C ± 2 ^{0}C / 75 % ± 5 % RH)

CONCLUSION

Fast disintegrating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. The dosage form had a good balance over disintegration time and mechanical strength. Amongst all formulations, formulation F4 prepared with croscarmellose sodium showed least dispersion time and faster dissolution. Thus it can be concludes that optimum concentration of super disintegrants is a promising approach to prepare fast disintegrating tablet of poorly water soluble nonsteroidal anti-inflammatory drug of Aceclofenac and such other poorly water soluble drugs.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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